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(57) **Abstract**

Technical problem V1 operation inhibitor of arginine vasopressin with which the moving state in the living body has been improved is offered having high V1 acceptor compatibility.

Means for Solution The triazole derivative shown by the general formula (I), or its salt permitted pharmaceutically.

Formula 1

(However, the radical as which R1 is expressed **alkyl group / a hydrogen atom, a halogen atom, or / low-grade** in formula-X-B for A ring in a formula in the benzene ring etc. is a substituent which may exist when R1 is a hydrogen atom or a low-grade alkyl group.) R3 shows a low-grade alkyl group etc., and R4 shows the low-grade alkyl group by which Y indicates N or CH to be and R2 may be permuted in the phenyl group permuted by the biphenyl or heterocycle, the alkoxyl group which may be permuted for a hydrogen atom etc.

Claim(s)

Claim 1 Physic characterized by containing the triazole derivative shown by the following general formula (I), or its salt permitted pharmaceutically.

Formula 1

(However, the notation in a formula has following semantics.)

The benzene ring or a thiophene ring A ring : An R1:hydrogen atom, a halogen

atom, The radical expressed with formula-X-B in a nitro group, the amino group, or a low-grade alkyl group : by the substituent which may exist when R1 is a hydrogen atom or a low-grade alkyl group It has following semantics. X:single bond, an oxygen atom, a -NHCO-radical, a -NHCONH-radical, - The aryl group which shows a NHCSNH-radical or a -(CH2) n-O-radical (n shows the integer of 1-5), and may be permuted by the B ring:low-grade alkyl group or the phenyl group Or the heterocycle radical which may be permuted by the low-grade alkyl group is shown. Y:N or CH is shown. An R2:permutation The low-grade alkyl group which may be carried out, A halogen atom, a hydroxyl group, a phenyl group, the alkoxyl group that may be permuted, The low-grade alkynyl group which may be permuted, or the amino group which may be permuted is shown. A hydrogen atom or a low-grade alkyl group is shown. R3 : An R4:low-grade alkyl group, A low-grade alkoxyl group and low-grade alkyl sulfonyl group, a halogen atom, the amino group, a cyano group, a trihalogeno methyl group, a nitro group, or the radical that may become together with R2 and may form a cycloalkyl radical is shown, and m shows zero or the integer of 1-3.

Claim 2 V1 acceptor antagonist of the arginine vasopressin characterized by containing a triazole derivative or its salt permitted pharmaceutically according to claim 1.

Claim 3 The therapy agent of the diabetic nephropathy characterized by containing a triazole derivative or its salt permitted pharmaceutically according to claim 1.

Claim 4 The triazole derivative shown by the following general formula (I), or its salt.

Formula 2

(However, the notation in a formula has following semantics.)

The benzene ring or a thiophene ring A ring : An R1:hydrogen atom, a halogen atom, The radical expressed with formula-X-B in a nitro group, the amino group, or a low-grade alkyl group : by the substituent which may exist when R1 is a hydrogen atom or a low-grade alkyl group It has following semantics. X:single bond, an oxygen atom, a -NHCO-radical, a -NHCONH-radical, - The aryl group which shows a NHCSNH-radical or a -(CH2) n-O-radical (n shows the integer of 1-5), and may be permuted by the B ring:low-grade alkyl group or the phenyl group Or the heterocycle radical which may be permuted by the low-grade alkyl group is shown. Y:N or CH is shown. An R2:hydrogen atom, the low-grade alkyl group which may be permuted, A halogen atom, a hydroxyl group, a phenyl group, the alkoxyl group that may be permuted (however, when Y is **R3** a methyl group in CH at non-permuted 4-biphenyl radical for the radical expressed with formula-X-B, R2 shows radicals other than methoxy.) The low-grade alkynyl group which may be permuted, or the amino group which may be permuted is shown. A hydrogen atom or a low-grade alkyl group is shown. R3 : An R4:low-grade alkyl group, a hydroxyl-group, low-grade alkoxyl group, and low-grade alkyl sulfonyl group, a halogen atom, the amino group, a cyano group, a trihalogeno methyl group, a nitro group, or the radical that may become together with R2 and may form a cycloalkyl radical is shown, and m shows zero or the integer of 1-3.

Detailed Description of the Invention

0001

Field of the Invention This invention relates to V1 acceptor antagonist of physis, the new triazole derivative which rivals V1 acceptor of arginine vasopressin especially or its salt permitted pharmaceutically, and the arginine vasopressin which makes

them an active principle.

0002

Description of the Prior Art Diabetic nephropathy is one of the three diabetic major complication, and the metabolic error centering on hyperglycemia is deeply involved in the onset progress. In current, before albuminuria, a diagnosis becomes possible at an early stage by the diagnosis by the minute amount albuminuria etc., and the needs for prevention and the therapy of initial diabetic nephropathy are increasing.

0003 In the diabetic or the diabetes-mellitus model animal, since the rise of the arginine vasopressin (it is hereafter indicated as AVP.) concentration in plasma is seen, it is suggested that AVP is participating in (Diabetes, 38 (1989), 54-57), and diabetes mellitus. Although AVP is a peptide which consists of a biosynthesis and nine amino acid secreted in a hypothalamic pituitary system and V1 and V2 acceptor is known as the acceptor Especially V1 acceptor Contraction of efferent arteriole (Am.J.Physiol.256 (1989) F274-F278), It participates in composition of prostaglandin E 2 kind (J. Hypertention 11 (1993) 127-134). Addition of a glomerulus is increased, participating in the multiplication of the mesangial cell by AVP further is known, and it is shown clearly that it is deeply involved in onset hatred of diabetic nephropathy. Moreover, there is a clinical report that OPC-21268 (compound of EP No. 382185 official report example 141) which is a V1 alternative antagonist has actually improved a NIDDM patient's albuminuria. As mentioned above, it is expected that V1 antagonist can turn into effective prevention / therapy agent of initial diabetic nephropathy.

0004 Moreover, since it became clear that vasopressin promotes powerfully production of a permeability factor (VPF) and/or an angiogenesis factor (VEGF) through V1 acceptor, the intervention to the formation process of the vascular lesion in various diseases, such as diabetic retinopathy, diabetic nephropathy, and arteriosclerosis, is pointed out recently (Biochimicaet Biophysica Acta 1243 (1995) 195-202). Therefore, V1 antagonist is useful for the prevention and the therapy of angiopathy in various diseases.

0005 On the other hand, V2 acceptor antagonist has the desirable compound which having a water diuretic effect is known and rivals the kidney disease accompanied by an edema at V1 and V two-car acceptor, and is the international public presentation WO as such a compound. 95/03305 and WO The bends azepine derivative indicated to 95/06035 is known. However, in the early diabetic nephropathy which has symptoms, such as a disease without an edema etc., for example, thirst, and polyuria, an alternative V1 acceptor antagonist is more desirable.

0006 Moreover, oxytocin is known as a peptide which is very similar to AVP and consists of a biosynthesis and nine amino acid secreted in a hypothalamic pituitary system, and it is known that a certain kind of AVP antagonist will cause operation inhibition of uterine contraction, a milk discharge operation, etc. also against this oxytocin acceptor.

0007 therefore, the disease in which V1 acceptor without edemata, such as angiopathy in early diabetic nephropathy or early various diseases, participates -- receiving -- V2 acceptor and an oxytocin acceptor -- receiving -- V -- it is expected that the compound which has more powerful antagonism alternatively 1 acceptor will serve as a good therapy agent.

0008

Problem(s) to be Solved by the Invention As a result of having advanced screening of the compound which has alternative and high V1 acceptor compatibility, on the basis of the above backgrounds, the artificers of this invention find out that a certain kind of specific triazole derivative fulfills the above-mentioned conditions, and came to complete this invention on it.

0009

Means for Solving the Problem This invention relates to the triazole derivative shown by the following general formula (I), or its salt permitted pharmaceutically.

0010

Formula 3

0011 (However, the notation in a formula has following semantics.)

The benzene ring or a thiophene ring A ring : An R1:hydrogen atom, a halogen atom, The radical expressed with formula-X-B in a nitro group, the amino group, or a low-grade alkyl group : by the substituent which may exist when R1 is a hydrogen atom or a low-grade alkyl group It has following semantics. X:single bond, an oxygen atom, a -NHCO-radical, a -NHCONH-radical, - The aryl group which shows a NHCSNH-radical, -, or a -(CH₂)_n-O-radical (n shows the integer of 1-5), and may be permuted by the B ring:low-grade alkyl group or the phenyl group Or the heterocycle radical which may be permuted by the low-grade alkyl group is shown. Y:N or CH is shown. An R2:hydrogen atom, the low-grade alkyl group which may be permuted, A halogen atom, a hydroxyl group, a phenyl group, the alkoxyl group that may be permuted, ** shows the amino group which may be permuted the low-grade alkynyl group which may be permuted, and as. A hydrogen atom or a low-grade alkyl group is shown. R3 : An R4:low-grade alkyl group, a hydroxyl-group, low-grade alkoxyl group, and low-grade alkyl sulfonyl group, a halogen atom, the amino group, a cyano group, a trihalogeno methyl group, a nitro group, or the radical that may become together with R2 and may form a cycloalkyl radical is shown, and m shows zero or the integer of 1-3.

0012

Embodiment of the Invention The triazole derivative concerning this invention is explained further. It is the thing whose X is single bond and whose B rings are a non-permuted aryl group, especially a phenyl group as substituent-X-B which may exist when A ring is the benzene ring among the triazole derivatives concerning this invention and R1 is hydrogen or low-grade alkyl, i.e., a bottom type, (II).

0013

Formula 4

0014 (-- however, A ring, B ring, and R1 and X express the respectively same semantics as the above in a formula.) -- a biphenyl radical and the compound which is especially 4-biphenyl radical have a desirable substituent in the 3rd place of the triazole ring expressed.

0015 Furthermore, when the substituent of the 3rd place is a biphenyl radical, as a substituent of the 4th place of a triazole ring, the phenyl group whose Y is CH is desirable, and that whose R2 of this substituent is the alkoxyl group which may be permuted is desirable especially. What the carbon numbers of an alkoxyl group are 2-10, and heterocycle has combined with the carbon atom of the end especially is desirable. As starting heterocycle, 4-permutation piperidino radical, a permutation piperidyl radical, 4-permutation piperazinyl radical, a permutation gay piperazinyl radical, a permutation AZEPANIRU radical, a morpholino radical, etc. are mentioned.

0016 Of course, the above-mentioned explanation is outlined about the compound applied to this invention taking the case of the case where the substituent expressed with the above-mentioned formula of the compounds concerning this invention (II) is a biphenyl radical. Therefore, this explanation does not cover all the compounds concerning this invention, either, and does not **** all desirable compounds, either.

0017 In addition, the word "low-grade" Becoming means the straight chain of 1-6

carbon numbers, or the hydrocarbon chain of the letter of branching among this specification.

0018 Therefore, as a "low-grade alkyl group", a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, etc. are specifically mentioned.

0019 As a "low-grade alkoxy group", a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, a pentyloxy radical, a hexyloxy radical, an iso hexyloxy radical, etc. are specifically mentioned. Moreover, specifically, in addition to the above-mentioned low-grade alkoxy group, a heptanoxyl radical, an octanoxyl radical, a nona NOKISHI radical, a deca NOKISHI radical, an undeca NOKISHI radical, a dodeca NOKISHI radical, or the branching alkoxy group that has the same carbon number as these is included as an "alkoxy group" including the alkoxy group to a carbon number 12.

0020 As a "halogen atom", a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned.

0021 They are the nitrogen-containing aromatic series 5 thru/or 6 member heterocycle radical at the "heterocycle radical" as a B ring machine. A pyrrolyl radical, a pylori nil radical, an imidazolyl radical, a PIRAZONIRU radical, a pyrazolyl radical, A pyrrolidinyl radical, a furil radical, a pyridyl radical, a pyrazinyl radical, a piperidyl radical, A pyrimidinyl group, a pilus DAJINIRU radical, a pyrrolidinyl radical, a tetrazolyl group, The piperidino radical a thoria ZORIRU radical, a thiazolyl radical, whose oxazolyl radical, etc. are the nitrogen-containing saturation 5 thru/or 8 member heterocycle radical further, a piperidyl radical, a morpholino radical, a mol HORINIRU radical, a piperazinyl radical, an imidazolyl radical, a gay piperazinyl radical, etc. are contained.

0022 A "low-grade alkynyl group" is an alkynyl group whose carbon number is 2-6 pieces. Specifically An ethynyl group, 1-propynyl radical, 2-propynyl group, 1-butylnyl radical, 2-butylnyl radical, 3-butylnyl radical, 1-methyl-2-propynyl group, 1-cutting-pliers nil radical, 2-cutting-pliers nil radical, 3-cutting-pliers nil radical, 4-cutting-pliers nil radical, A 3-methyl-1-butylnyl radical, a 2-methyl-3-butylnyl radical, a 1-methyl-2-butylnyl radical, 1-methyl-3-butylnyl radical, 1, and 1-dimethyl-2-propynyl group, 1-hexynyl group, 2-hexynyl group, 3-hexynyl group, 4-hexynyl group, 5-hexynyl group, etc. can be mentioned. As a substituent of a "low-grade alkynyl group", a hydroxyl group, "the alkoxy group which may have the substituent" explained in full detail below in addition to a halogen atom etc., etc. are mentioned.

0023 What has the substituent in which above-mentioned heterocycle and this heterocycle contain heterocycle and a low-grade alkyl group further as a substituent of "the alkoxy group which may be permuted" is mentioned. Furthermore, the phenyl group which may have a substituent is contained. As a substituent of the above-mentioned phenyl group, 4-low-grade alkyl piperazinyl carbonyl etc. is mentioned. The following is mentioned as a concrete example of such "an alkoxy group which may be permuted." A phenylalkoxy radical, a phenylalkoxy (4-alkyl piperazine-1-yl-carbonyl) radical, A phenylalkoxy radical, a phenylalkoxy (piperidino carbonyl) radical, (4-piperidino piperidino carbonyl) An alkoxy group, an alkoxy group (4-piperidino piperidino carbonyl), (4-alkyl piperazine-1-yl-carbonyl) An alkoxy group, an alkoxy group (morpholino carbonyl), (Piperidino carbonyl) An alkoxy group, an alkoxy group (hydroxy carbonyl), (Alkoxy carbonyl) A **(4-alkyl piperazine-1-IRU) alkylamino carbonyl** alkoxy group, A **4-(pyrimidine-2-IRU) piperazine-1-IRU** alkoxy group, A **4-(2-pyridyl) piperazine-1-IRU** alkoxy group, an alkoxy group (4-alkyl piperazine-1-IRU), An alkoxy group, an alkoxy group (4-piperidino piperidino), (4-alkyl gay piperazine-1-IRU) A **(piperidinyl-1-IRU) alkylamino** alkoxy group, a piperidino alkoxy group, A piperidyl alkoxy group, a

morpholino alkoxy group, a pyridyl alkoxy group, an imidazolyl alkoxy group, an alkoxy group (2-amino phenoxy), a hydroxy alkoxy group, etc. are mentioned.

0024 As "an amino group which may be permuted", the amino group permuted by the alkyl group of a low-grade alkyl group, i.e., the shape of a straight chain of 1-6 carbon numbers, or the letter of branching is sufficient. Moreover, the heterocycle which contains a nitrogen atom with other substituents may be formed, and the above heterocycles illustrated as a B ring are included as such heterocycle.

Moreover, such heterocycles may have the substituent further and what acid residue, such as a low-grade alkyl group, and an acetic acid, a propionic acid, combined with the nitrogen atom of the 4th place of heterocycle is contained as an amino group which has such a substituent.

0025 Specifically as a cycloalkyl radical formed from R4 combined with R2 and the ortho position, cyclo butyl, a cyclopentyl group, a cyclohexyl radical, a cycloheptyl radical, a cyclo octyl radical, etc. are mentioned.

0026 It is the case where A ring is a phenyl group, and the following is mentioned as a concrete example of the substituent which consists of this ring and formula-X-B. A phenoxyphenyl radical, a phenylalkoxy phenyl group, a carbonyl (2-biphenyl) aminophenyl radical, The biphenyl radical which may be permuted by the low-grade alkyl group, the furil carbonylamino phenyl group which may be permuted by the low-grade alkyl group, A biphenyl radical, a piperidino phenyl group, a phenyl group (piperidino alkoxy), The pyrrolidinyl phenyl group which has a substituent and may be, the imidazolyl phenyl group which has a substituent and may be, The thiazolyl phenyl group, morpholino phenyl group which have a substituent and may be, (Morpholino alkoxy) A phenyl group, the phenyl ureylene phenyl group which may be permuted by the low-grade alkyl group, the phenylthio ureylene phenyl group which may be permuted by the low-grade alkyl group, a phenoxyphenyl radical, a phenylthiophenyl radical, etc. are mentioned.

0027 An "aryl group" is an aryl group of carbon numbers 6-14 preferably, and, specifically, a phenyl group, a biphenyl radical, a naphthyl group, an anthryl radical, a phenanthryl group, etc. are mentioned.

0028 An inorganic acid or an organic acid, and a salt may be able to be formed, and, as for this invention compound, those salts also have V1 operation inhibitory action. As a suitable salt, for example A hydrochloric acid, a hydrobromic acid, a hydroiodic acid, a sulfuric acid, A salt with mineral acids, such as a nitric acid or a phosphoric acid, a formic acid, an acetic acid, a propionic acid, oxalic acid, A malonic acid, a succinic acid, a fumaric acid, a maleic acid, a lactic acid, a malic acid, a tartaric acid, A citric acid, carbonic acid, glutamic acid, an aspartic acid, methanesulfonic acid, A salt with organic acids, such as ethane sulfonic acid, sodium, a potassium, magnesium, A salt with basic amino acid, such as a salt with organic bases, such as a salt with inorganic bases, such as calcium and aluminum, monomethylamine, ethylamine, and ethanolamine, a lysine, and an ornithine, etc. can be mentioned. Moreover, although quaternary ammonium salt can also be formed at a reaction with low-grade alkyl halide, low-grade alkyl trifluoromethanesulfonate, low-grade alkyl tosylate, or benzyl halide, as quaternary ammonium salt, a salt with a methyl iodide or benzyl chloride is desirable.

0029 When the optical isomer based on an asymmetric carbon atom and the geometrical isomer based on a double bond or a cyclohexane ring may exist and it has two or more asymmetric carbon atoms, a diastereoisomer exists in this invention compound further. The mixture of the thing from which these various isomers were isolated, and these isomers is contained in this invention. Moreover, a hydrate, various solvates, a tautomer, etc. are contained in this invention compound. Furthermore, there is also a compound which has a crystal polymorphism among this invention compounds, and all of those crystal form are included by this invention

compound.

0030 In a general formula (I), R4 is a hydrogen atom, R3 is a methyl group and R2 is **Y is CH and** the substituent which consists of an A ring and formula-X-B is non-permuted 4-biphenyl radical, and new **the compound which is a medicinal active principle concerning this invention** except for the thing of a methoxy group. Y is CH, R4 is a hydrogen atom and, as for this thing, R2 is **the thing of a methoxy group is also compounded by the lab test company (Germany fly BERUGU city), and** R3 is a methyl group and more nearly available **the substituent which consists of an A ring and formula-X-B in the above-mentioned formula (I) is non-permuted 4-biphenyl radical, and** than a lab test company by claim.

0031 (Manufacturing method) The manufacturing method of the compound applied to this invention below is explained. 3, the 4-diaryl permutation-5-permutation which are a basic frame - 1, 2, and 4-triazole derivative (7) can be manufactured by two approaches usually shown below. First, **whether as the 1st approach, as shown in the bottom type-ization 5, aromatic carboxylic acid (1) is condensed in inert solvents, such as a tetrahydrofuran and an acetonitrile, as an aromatic series carvone acid chloride activated by the thionyl chloride etc., and** Or the acid hydrazide obtained by making aromatic series carboxylate react in the hydrazine of 10 equivalence, and alcohol (4), **whether condensation is carried out to acylating agents, such as an acetic anhydride, under existence of organic bases, such as a pyridine, and** Or a diacyl hydrazine (5) is obtained by making an aromatic series carvone acid chloride (2) react with direct acid hydrazide. Ring closure of the diacyl hydrazine (5) obtained in this way is carried out under existence of dehydrating agents, such as a phosphorus pentaoxide. 1, 3, and 4-oxazole (6) can be obtained and 1, 2, and 4-triazole derivative (7) which targets this by carrying out heating reflux in solvents, such as toluene, under existence of the acid catalyst of heating or a tosyl acid with an aniline derivative and a non-solvent can be obtained.

0032

Formula 5

0033 In addition, about the manufacture approach of a diacyl hydrazine (5), it is E.Klinsberg. J. Am. Chem. Soc., 1958 and 80, and 5786-5789, please refer to if needed. Moreover, as an acid catalyst used in the case of heating reflux, a mesyl acid, a camphor sulfonic acid, etc. can be used in addition to a tosyl acid, and a xylene, monochrome, or a dichlorobenzene can be used as a solvent in addition to toluene.

0034 As the 2nd approach, as shown in the bottom type-ization 6, carry out condensation of the aniline derivative (8) in acylating agents, such as an acetic anhydride, and organic solvents, such as a tetrahydrofuran, and an anilide (9) is obtained. The thioamide (10) which thioamide-ized this using phosphorus pentasulfide in organic solvents, such as toluene, obtained the thioamide (10), and was obtained in this way by the methyl iodide as S-methylthio imidate (11) The pyrogenetic reaction of this is carried out to acid hydrazide (4) at 120 degrees C among dimethyl formaldehyde (Following DMF may be called). 1, 2, and 4-triazole derivative (7) is obtained, or a compound (8) can be made to be able to heat with ortho acid ester, it can consider as O-alkyl imidate (12), this can be made to be able to react like acid hydrazide (4) and the above, and 1, 2, and 4-triazole derivative (7) can be obtained. As a solvent, as for the reaction with acid hydrazide (4), dimethylacetamide, DMSO, a 1-methyl-2-pyrrolidone, etc. are suitably used in addition to DMF.

0035

Formula 6

0036 Next, the conversion approach of the side chain of R2 grade is explained. As the conversion approach of a side chain, the approach shown in the bottom type-ization 6 is mentioned. That is, a benzyloxy derivative (7) is debenzylated in catalytic reduction, a phenol derivative compound (13) is obtained, to this, at the Mitsunobu reaction with alkyl halide, alkyl sulfonate, or alcohol, an alkyl group is introduced and an alkoxy phenyl triazole derivative (14) is obtained. Moreover, alkylene dihalide and a phenol derivative compound (13) are made to react, it considers as a halogeno alkoxy phenyl triazole derivative, and an amino alkoxy phenyl triazole derivative is obtained by giving this to a substitution reaction with an amine. Moreover, an iodine object (15) is given to a **** reaction ($\text{PdCl}_2(\text{PPh}_3)_2$, CuI and PPh_3 , acetylene / Et_3N -pyridine), an alkylene derivative (16) is obtained, and an alkylphenyl triazole derivative (17) is obtained by giving this to catalytic reduction.

0037

Formula 7

0038 In addition, like the above, isomers, such as racemic modification, the optically active substance, and a diastereomer, may be independent to this invention compound, or may exist in it as mixture. A racemic compound can be led to an isomer pure in stereochemistry by using a suitable raw material compound or the general optical resolution method (for example, the approach of drawing and carrying out optical resolution to diastereomeric salt with common optical-activity acids (tartaric acid etc.)). Moreover, the mixture of a diastereomer is separable with a conventional method, for example, fractional-crystallization-izing, or a chromatography.

0039

Effect of the Invention To V2 acceptor and oxytocin acceptor of AVP, this invention compound rivals V1 acceptor of AVP alternatively, for example, has vasodilatation, a blood-pressure descent operation, a cardiac hyperergasia operation, cardiac muscle cell hypertrophy depressant action, blood vessel smooth muscle growth / hypertrophy depressant action, mesangial cell growth / hypertrophy depressant action, mesangial cell contraction depressant action, platelet aggregation depressant action, a permeability factor (VPF) / angiogenesis factor (VEGE) production depressant action, endothelin production depressant action, liver glyconeogenesis depressant action, etc.

0040 moreover, the operation over AVP of this invention compound -- V -- 1 acceptor, since it is alternative Without being accompanied by operation of the uterine contraction based on the water diuretic effect based on V2 acceptor antagonism, or oxytocin acceptor antagonism etc. It can use for the treatment of many diseases in which V1 acceptor of AVP participates. For example, are useful as vasodepressor, a hypotensor, an anti-cardiac insufficiency agent, an anti-renal failure agent, a platelet aggregation inhibitor, etc. It is effective in prevention and the therapy of hypertension, cardiac insufficiency, kidney disease, the cerebrovascular disease, diabetes mellitus, diabetic nephropathy, diabetic retinopathy, various ischemic diseases, circulatory failure, arteriosclerosis, a gastric ulcer, nausea, vomiting, a faint, a malignant tumor, cancer, renal dysfunction, etc. Especially, it is useful for prevention and the therapy of early diabetic nephropathy. Moreover, this invention compound has **that it excels in oral absorbency and is moreover hard to receive a metabolic turnover in the living body** good durability.

0041 The example of an experiment explains below the pharmacological action

which this invention compound has.

0042 V1 antagonism in a non-anesthetized rat (internal use)

V1 antagonism was considered using the Wistar system male rat (weights 300-320g) which inserted the cannula for blood pressure measurement in the left carotid artery, and inserted the cannula for AVP administration in the left jugular vein beforehand two - three days before experiment initiation. Blood pressure was measured under no anesthetizing through the pressure transducer from arterial cannula. The test compound was suspended in the methyl cellulose solution 0.5%, and it administered orally by the dosage of 1, 10, and 100 mg/kg.

0043 The rise of the diastolic blood pressure by the AVP30 mU/kg intravenous administration before test compound administration was made into 100%, and 8 hours after after **of test compound administration** 30 minutes, the pressure up by AVP30 mU/kg intravenous administration was measured periodically, and it considered as V1 antagonism of a test compound in quest of the rate of control of the pressure up by the test compound. Consequently, V1 antagonism powerful **this invention compound** and continuous was shown.

0044 Using the support and the excipient for pharmaceutical preparation which are usually used, and other additives, the physic constituent which contains one sort, such as a compound shown by the general formula (I), and the salt permitted pharmaceutically or a hydrate, or two sorts or more as an active principle is prepared by a tablet, powder, a fine grain agent, a granule, a capsule, a pill, liquids and solutions, injections, suppositories, ointment, patches etc. be prescribed for the patient taking-orally-wise or parenterally

0045 Although the clinical dose to the Homo sapiens of this invention compound is suitably determined according to each case in consideration of a patient's symptom applied, age, sex, weight, etc., it is usually 0.1-500mg in adult 1 sunny taking orally, and this is prescribed for the patient in 1 time or several steps. Since a dose is changed on condition that versatility, an amount smaller than the above-mentioned dose range may be enough as it.

0046 A tablet, powder, a granule, etc. are used as a solid-state constituent for internal use by this invention. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, magnesium aluminometasilicate, etc.

0047 The constituent may contain the solubilization or the solubilizing agent like additives other than an inactive diluent, for example, lubricant like magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. The coat of a tablet or the pill may be carried out as occasion demands with the film of stomach solubility, such as cane sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or the enteric matter. The liquid constituent for internal use contains the inactive diluent generally used, for example, purified water, and ethyl alcohol including the opacifier permitted in drugs, a solution agent, suspension, syrups, elixirs, etc. This constituent may contain solubilization thru/or a solubilizing agent, a wetting agent, an adjuvant like suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent.

0048 As injections for parenteral administration, the solution agent of sterile aquosity or nonaqueous nature, suspension, and an opacifier are included. As a water solution agent and a diluent of suspension, distilled water for injections and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethyl alcohol, a surfactant like polysorbate 80 (trade name), etc., for example. Such a constituent may also contain an additive still

like an isotonicizing agent, antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), solubilization, or a solubilizing agent (for example, glutamic acid, an aspartic acid). These are sanitized by the filtration which lets for example, a bacteria hold filter pass, combination of a germicide, or exposure. These manufacture a sterile solid-state constituent again, and they can also use it for non-bacterial water or the sterile solvent for injection before use, dissolving.

0049

Example Hereafter, and this invention is further explained to a detail. **an example** In addition, it cannot be overemphasized that this invention is not limited only to the compound of an example. Furthermore, when the raw material used by this invention is new, it explains as an example of reference.

0050 (Example 1)

4-(2-methoxyphenyl)-3-(4'-biphenyl)- 1, 2, and 4-triazole (compound number 22) 3-(4'-biphenyl)- 1, 3, and 4-OKISA diazole (538mg) and o-anisidine (6ml) were heated at 150 degrees C with the non-solvent for 12 hours. The silica gel column chromatography refined the reaction mixture, and it was obtained 95mg (12%), having used the title compound as the brown solid. The NMR data of the obtained compound are as follows.

3.63 (3H, s), 7.11 (1H, t, J= 7.5Hz), 7.25 (1H, d, J= 8.4Hz), 7.35-7.57 (7H, m), 7.67-7.69 (4H, m), 8.72(1H, s) **0051** (Example 1 of reference)

N-(2-benzyloxyphenyl) acetamide acetic anhydride (20ml) was added to the ethyl-acetate (100ml) solution of 2-aminophenol (10.91g) under the room temperature, and was stirred for 30 minutes. Ethyl acetate was added to residue after condensing reaction mixture, and the crystal was ****(ed). This crystal, benzyl bromide (18.8g), and the acetonitrile (300ml) mixed liquor of potassium carbonate (30.0g) were stirred at 70 degrees C all night. Ethyl acetate was added for reaction mixture to residue after ****, water and saturation brine washed this and it was condensed after desiccation. The silica gel column chromatography refined residue, and it was obtained 22.64g (94%), having used the title compound as the white solid. The physical properties of this thing are as follows.

FAB-MS m/z: 242(M++H).1 H-NMR (CDCl3) delta: -- 2.15 (3H, s), 5.12 (2H, s), 6.92-7.05 (3H, m), and 7.35- 7.48 (5H, m), 7.76 (1H, br s), and 8.30-8.40(1H, m).

0052 (Example 2 of reference)

An N-(2-benzyloxyphenyl)-S-methyl aceto thio imidate N-(2-benzyloxyphenyl) acetamide (22.55g) and the toluene (300ml) mixed liquor of phosphorus pentasulfide (23.0g) were stirred at 70 degrees C for 2 hours. It condensed after separating a part for the supernatant of reaction mixture, and the silica gel column chromatography refined residue, and it was obtained 11.51g, having used N-(2-benzyloxyphenyl) thioacetamide as the brown liquid. The acetonitrile (300ml) mixed liquor of this, a methyl iodide (20.0g), and potassium carbonate (30.0g) was stirred at 50 degrees C for 3 hours. Ethyl acetate was added for reaction mixture to residue after ****, water and saturation brine washed this and it was condensed after desiccation. The silica gel column chromatography refined residue, and it was obtained 16.23g (64%), having used the title compound as the red liquid. The physical properties of this thing are as follows.

FAB-MS m/z: 272(M++H).1 H-NMR (CDCl3) delta: 1.97 (3H, s), 2.46 (3H, s), 4.99 (2H, s) and 6.65 (1H, d, J= 10Hz), 6.90-7.08 (3H, m), 7.28-7.49(5H, m). **0053** (Example 3 of reference)

The ethanol (100ml) mixed liquor of biphenyl-4-carboxylic-acid hydrazide biphenyl-4-carboxylic-acid ethyl (2.26g) and a hydrazine and 1 hydrate (5.0g) was agitated at 170 degrees among the sealed tube container all night. The ethyl acetate after concentration was added for reaction mixture, the crystal was separated, and it was obtained 1.59g (75%), having used the title compound as the white solid. The

physical properties of this thing are as follows.

FAB-MS m/z: 213(M++H). 1 H-NMR (CDCl₃) delta: 4.52 (2H, br s), 7.30-7.60 (3H, m), 7.60-7.90 (4H, m), 7.90-8.00 (2H, m), 9.83 (1H, br s). **0054** (Example 2)

4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl - The dimethylformamide (DMF, 3ml) solution of 1, 2, 4-triazole (compound number 39) N-(2-benzyloxyphenyl)-S-methyl aceto thio imidate (300mg), and 4-biphenyl carboxylic-acid hydrazide (212mg) was stirred at 120 degrees C for 2 hours. Ethyl acetate was added for reaction mixture to residue after ****, water and saturation brine washed this and it was condensed after desiccation. The silica gel column chromatography refined residue and it crystallized with hexane-ethyl acetate, and it was obtained 275mg (66%), having used the title compound as the white solid. The NMR data of this thing are as follows.

2.31 (3H, s), 4.95 (1H, d, J= 13Hz), 5.06 (1H, d, J= 13Hz), 6.95-7.15 (4H, m), 7.20-7.60 (14H, m) / CDCl₃ **0055** (Example 3)

2-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole-4-IRU phenol (compound number 43) 4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl - The DMF (50ml) mixed liquor of 1, 2, 4-triazole (2.78g), and 10% palladium-carbon (0.50g) was stirred under the room temperature all night. Reaction mixture was condensed after *****, ethyl acetate was added to residue, the crystal was ****(ed), and it was obtained, having used the title compound as the gray solid (2.05g). The NMR data of this thing are as follows.

2.17 (3H, s), 6.95 (1H, t, J= 8Hz), 7.07 (1H, t, J= 8Hz), 7.30-7.53 (7H, m), 7.60-7.65 (4H, m), 10.33 (1H, s)/DMSO-d₆ **0056** (Example 4 of reference)

4-2-(6-BUROMO hexyloxy) phenyl-3- (4'-biphenyl) -5-methyl - 1, 2, 4-triazole **2-3-(4'-biphenyl)-5-methyl - 1, 2, a 4-triazole-4-IRU** phenol (1.04g), The acetonitrile (50ml) mixed liquor of 1, 6-dibromo hexane (3.90g), and potassium carbonate (3.0g) was stirred at 50 degrees C for 30 minutes. Ethyl acetate was added for reaction mixture to residue after ****, water and saturation brine washed this and it was condensed after desiccation. The silica gel column chromatography refined residue, and it was obtained 1.22g (77%), having used the title compound as amorphous. The physical properties of this thing are as follows.

FAB-MS m/z: 492.(M++H) 1 H-NMR delta: 1.15-1.35 (4H, m) (CDCl₃), 1.50-1.65 (2H, m), 1.68-1.90 (2H, m), 2.29 (3H, s) and 3.31 (2H, t, J= 7Hz), and 3.75- 3.99 (2H, m), 7.06 (2H, t, J= 8Hz), and 7.15-7.60 (13H, m)

0057 (Example 4)

4-{2-6-methyl piperazine-1-IRU phenyl}-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole (compound number 54) 4-(2-(6-BUROMO hexyloxy) phenyl)-3-(4'-biphenyl)-5-methyl - 1 Two, The acetonitrile (20ml) mixed liquor of 4-triazole (0.60g), 1-methyl piperazine (200mg), and potassium carbonate (2.0g) was stirred at 70 degrees C for 2 hours. The chloroform methanol (10:1) was added for reaction mixture to residue after ****, water and saturation brine washed this and it was condensed after desiccation. The silica gel column chromatography refined residue and it crystallized with hexane-ethyl acetate, and it was obtained 420mg (69%), having used the title compound as the white solid. The NMR data of this thing are as follows.

1.18-1.23 (4H, m), 1.35-1.44 (2H, m), 1.51-1.60 (2H, m), 2.22-2.30 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 2.42 (6H, brs), 3.80-3.87 1H, m, 3.91-3.98 (1H, m), and 7.02-7.07 (2H, m), 7.17 (1H, dd, J= 1.7Hz, 7.7Hz), and 7.31-7.56 (10H, m) / CDCl₃

0058 (Example 5)

4-{2-4-(4-piperidyl) butoxy phenyl}-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole (compound number 72)

2-3-(4'-biphenyl)-5-methyl - 1, 2, a 4-triazole-4-IRU phenol (440mg), **4-4-(1-trityl) piperidyl** butyl The acetonitrile (10ml) mixed liquor of toluenesulfonate

(890mg) and potassium carbonate (2.0g) was agitated at 80 degrees C for 3 hours. After filtering reaction mixture, filtrate was condensed, the silica gel column chromatography refined residue, and 1.01g (quant.) of N-trityl objects of a title compound was acquired. Among these, deprotection of the 500mg was carried out in hydrochloric-acid-ethanol-ethyl acetate, and 220mg (67%) of title compounds was obtained. The NMR data of this thing are as follows.

0.90- 1.75 (11H, m), 2.30 (3H, s), 2.55-2.85 (2H, m), 3.00-3.25 (2H, m), 3.80-4.05 (2H, m), and 7.10- 7.80 (13H, m), 8.81 (1H, br), and 9.05 (1H, br)/DMSO-d₆ **0059** (Example 6)

4-{2-3-(3-pyridyl) propyl phenyl}-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole (compound number 85)

2-3-(4'-biphenyl)-5-methyl - The bottom diethyl azodicarboxylate (210mg) of ice-cooling was added to 1, 2, a 4-triazole-4-IRU phenol (220mg), 3-(3-pyridyl) propanol (140mg), and the THF (5ml) solution of triphenyl phosphine (310mg), and it agitated for 20 minutes. The silica gel column chromatography refined residue for the residue after concentration, reaction mixture was crystallized with hexane-ethyl acetate, and it was obtained 156mg (52%), having used the title compound as the white solid. The NMR data of this thing are as follows.

1.75- 1.95 (2H, m), 2.32 (3H, s), 2.30-2.60 (2H, m), 3.75-4.00 (2H, m), and 6.95-7.60 (15H, m), 8.30 (1H, s), and 8.39 (1H, d, J= 5Hz)/CDCl₃ **0060** (Example 7)

4-(2-{2-4-(4-methyl piperazine-1-IRU) carbonyl phenyl ethynyl} phenyl)-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole (compound number 41)

4-(2-iodation phenyl)-3-(4'-biphenyl)-5-methyl - The mixed liquor of 1, 2, 4-triazole (1.30g), triethylamine (10ml), a pyridine (4ml), copper iodide (56mg), dichlorobis (triphenyl phosphine) palladium (104mg), and triphenyl phosphine (780mg) was agitated at 70 degrees C all night. After filtering reaction mixture, it condensed, the silica gel column chromatography refined residue, and it crystalized with hexane-ethyl acetate, and it was obtained 1.22g (68%), having used the title compound as beige powder. The NMR data of this thing are as follows.

2.25-2.47 (4H, m), 2.33 (3H, s), 2.38 (3H, s), 3.42 (2H, brs) and 3.79 (2H, brs), 7.30-7.58 (17H, m) / DMSO **0061** (Example 8)

4-(2-{2-4-(4-methyl piperazine-1-IRU) carbonyl phenyl ethyl} phenyl)-3-(4'-biphenyl)-5-methyl - 1, 2, 4-triazole (compound number 41)

4-(2-{2-4-(4-methyl piperazine-1-IRU) carbonyl phenyl ethynyl} phenyl)-3-(4'-biphenyl)-5-methyl - 1, 2, and 4-triazole (1.09g) was given to catalytic reduction for three days by making 10% palladium-carbon (700mg) into a catalyst among the methanol (30ml). The silica gel column chromatography refined residue after filtering reaction mixture, and it crystallized with hexane-ethyl acetate, and it was obtained 1750mg (67%), having used the title compound as white powder. The NMR data of this thing are as follows.

2.20-2.65 (8H, m), 2.23 (3H, s), 2.30 (3H, s), 3.41 (2H, brs), 3.75 (2H, brs) and 6.93 (2H, d, J= 7.8Hz), 7.17-7.56 (15H, m) / DMSO **0062** Moreover, the structure

expression of a typical compound of the new triazole compound applied to this invention including the compound obtained in the above-mentioned example is shown in the following tables 1-16 with the physical properties. Moreover, the NMR data is also ***** to Tables 17-23 focusing on what displayed physical properties as the amorphism crystal among compounds other than the compound indicated in the example. In addition, the compound except having made it the publication as well as **almost** an approach given in said manufacturing method and example can apply some strange method obvious to this contractor to an example at them, or it can manufacture easily.

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Table 22
